Let's talk about Katherine

Eric P. Winer
Dana-Farber Cancer Institute
Brigham and Women's Hospital
Harvard Medical School
December 5, 2018

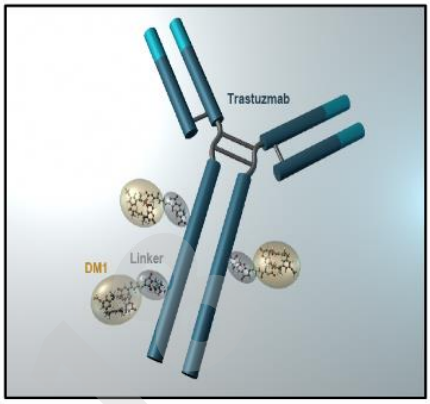
Disclosures

- Lilly – advisor board
- Roche – advisory board
- Jounce – advisor board
- GSK – advisor board

- LEAP – scientific advisory board
- VERASTEM – former member scientific advisory

Trastuzumab Emtansine

- First antibody drug conjugate approved in a solid tumor
- Trastuzumab connected via linker to small dose of emtansine (DM-1), a microtubule inhibitor 400-fold more potent than paclitaxel
- High affinity antibody and powerful payload
- Mechanism of action
  - Targeted delivery of chemotherapy
  - Anti-HER2 activity
- Limited toxicity
  - Limited toxicity because of low systemic DM1 levels
  - Rare liver toxicity
  - Thrombocytopenia
  - Mild fatigue

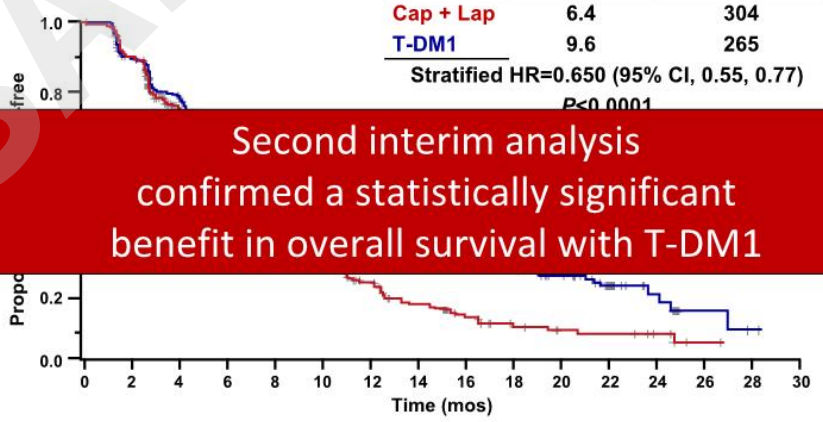


EMILIA: T-DM1 vs Capecitabine/Lapatinib in Second Line Setting

	Median (mos)	No. events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)

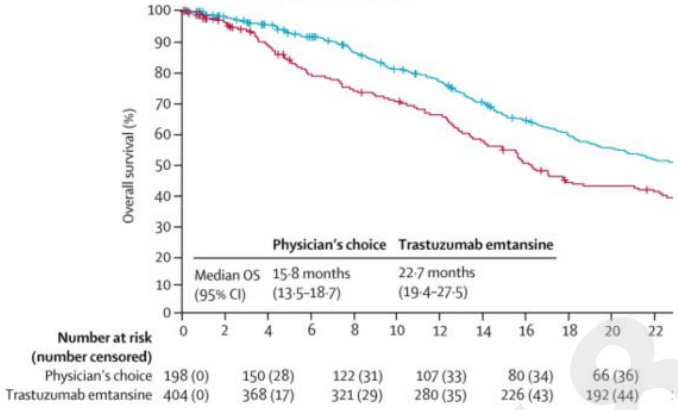
P<0.0001



Second interim analysis confirmed a statistically significant benefit in overall survival with T-DM1

Blackwell et al, NEJM 2012

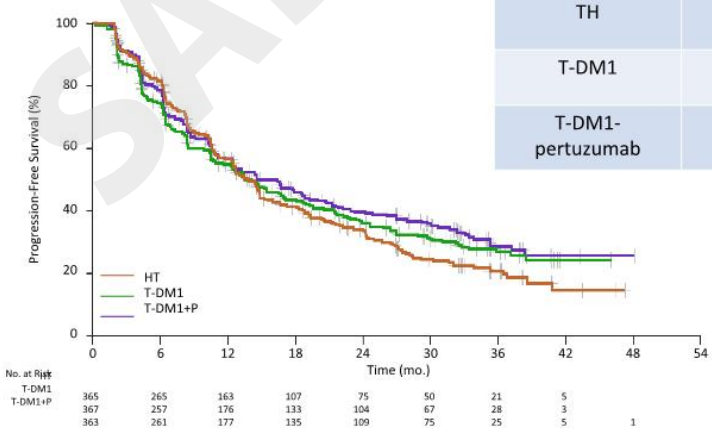
Survival Advantage T-DM1 vs. Physician Choice



Krop et al, Lancet Oncology 2017

MARIANNE Progression-Free Survival

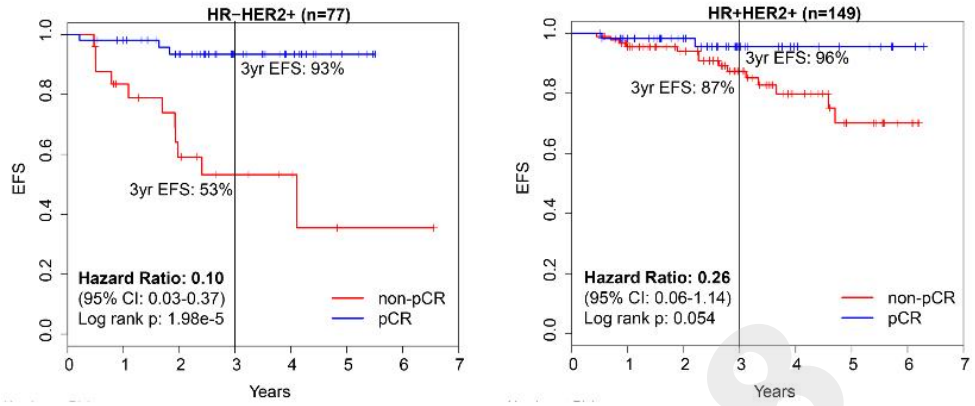
Regimen	Progression Free Survival (months)	P value compared to TH
TH	13.7	--
T-DM1	14.1	0.31
T-DM1-pertuzumab	15.2	0.14



- To some degree, Maryanne made many less enthusiastic about T-DM1
- Suggested no added benefit of pertuzumab to T-DM1

Perez et al, JCO 2017

Influence of pCR on EFS in HER2+ Disease: I-SPY



Difference between pCR vs. residual disease greater for ER- and ER+ consistent with meta-analysis from Cortazar et al, Lancet 2014

Yee et al, SABCS 2017

KATHERINE Study Design

- Centrally confirmed HER2-positive breast cancer
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Received neoadjuvant therapy consisting of
  - Minimum of 6 cycles of chemotherapy
    - All chemotherapy as neoadjuvant therapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylators allowed
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Pathologic residual invasive tumor in breast or axilla
- Randomization within 12 weeks of surgery

R 1:1

N=1486

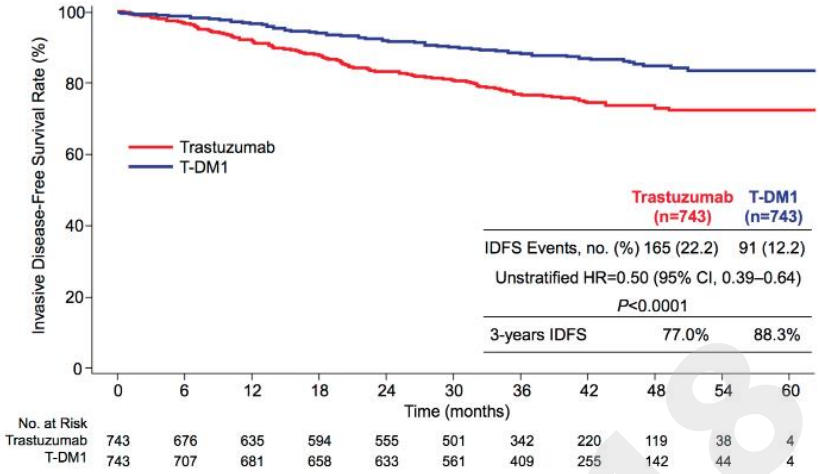
T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

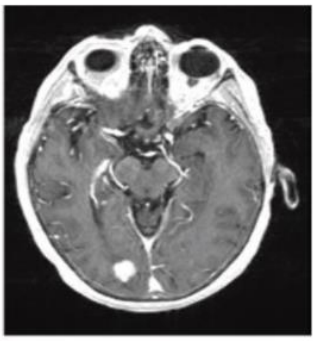
Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Invasive Disease-Free Survival



Unfortunately, there was no impact whatsoever on the incidence of brain metastases

Additional Research Urgently Needed



Some Additional Details and Caveats

- Most patients received anthracyclines and relatively few had pertuzumab
- The absolute benefit in patients with negative nodes and tumors 1 cm and less was modest, but still clinically significant
- The result was seen in spite of the fact that over 70% had ER+ disease
  - ER+ disease does not have as poor a prognosis in setting of residual disease
  - ER+ may be more heterogeneous and have lower level HER2 expression
- The result demonstrates that residual disease was often still HER2-driven

The Standard of Care Has Changed:

T-DM1 should be recommended to the vast majority of patients with residual disease after a taxane-based neoadjuvant regimen

Most Successful Trials Raise Questions

1. Questions about practical use of T-DM1 on Monday

2. Questions about how to design future trials and whether T-DM1 should play a more prominent role in early stage breast cancer

What if the patient received preoperative pertuzumab?

- Hazard ratio was almost identical irrespective of pertuzumab use
- If a patient does not have pCR in spite of pertuzumab, it is unlikely that continuing pertuzumab would be better than a switch, given modest improvement in Aphinity
- If pertuzumab is given preop, should it be continued with T-DM1?
  - No direct data, and I would not continue pertuzumab with T-DM1 now
  - BUT, in spite of Marianne results, pertuzumab could possibly add to T-DM1

Is it critical to administer 14 cycles of T-DM1?

- For some patients, this will mean more than a year of anti-HER2 treatment
- HOWEVER, the results were achieved with 14 cycles which should be the standard approach
- If a patient is having trouble with toxicity, she may need to stop sooner, but I would push for at least one full year of anti -HER2 treatment

Is there a role for Neratinib in patients with residual disease?

- Data for T-DM1 in Katherine directly address residual disease setting and are strong
- No data for Neratinib after T-DM1
- BOTTOM LINE: Although role uncertain, it is difficult to be enthusiastic about Neratinib in this population given Katherine result

What are the implications for clinical trials and clinical practice in early stage disease?

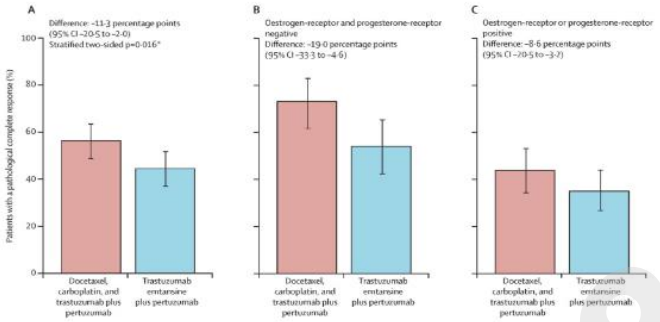
- What additional trials should be done with T-DM1 in early stage disease?
- What role should pertuzumab play in such trials?
- Is there still a role for anthracyclines in regimens of the future?
  - -- With another active agent in early disease, anthracyclines become less appealing

A Critical Question

Are we hitting a ceiling on effectiveness, and, if so, perhaps our research efforts be focused on:

- Designing the best tolerated regimens
- Conducting in depth translational studies on the tumors and host in the small minority with systemic recurrences?

TCHP vs T-DM1-P in Preoperative Setting: Kristine Trial



It will be important to see if the difference in pCR leads to any change in DFS/OS but even if DFS better for TCHP, does not rule out additive role for T-DM1

Hurvitz et al, Lancet Oncology 2018

Kaitlin Trial

HER2+ (centrally confirmed)
Node Positive
Node Negative if >2cm and HR-

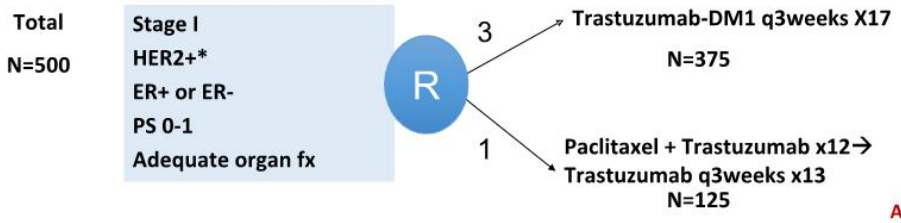
→ AC or EC x 4 → THP x 12 → HP x 13 doses

→ AC or EC x 4 → T-DM1 + P x 17 doses

N = approximately 2000

Results in next 1-2 years

ATEMPT Trial
TBCRC and Dana-Farber



ACCRUAL COMPLETED 2016

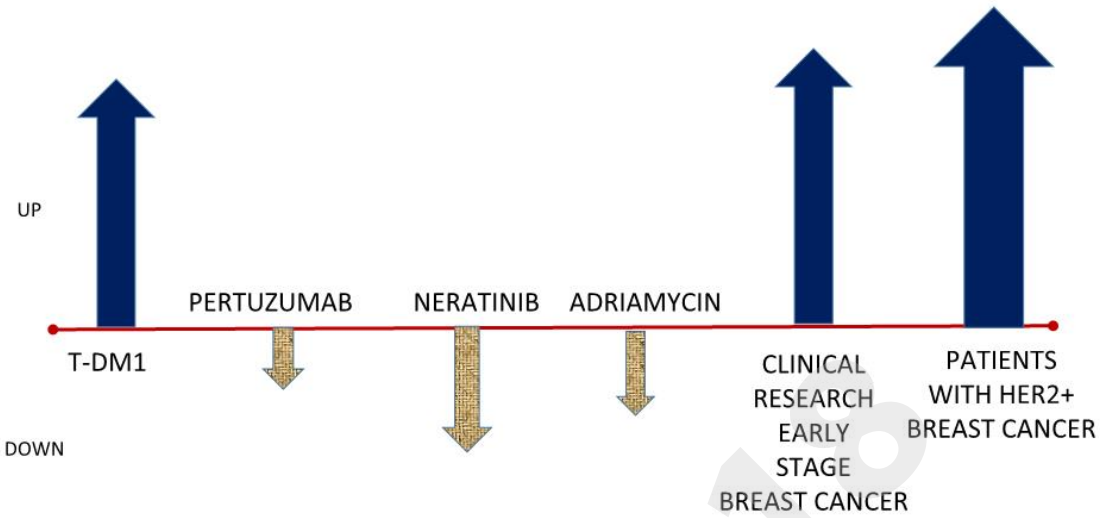
- **All HER2 testing centrally confirmed**
- **Adjuvant endocrine therapy can be initiated after completion of 12 weeks of therapy**
- **Adjuvant radiation therapy can be administered concurrently with study treatment.**

PI: Sara Tolaney, MD, MPH
Co-I: Ian Krop, MD, PhD
Eric Winer, MD

At the present time, the role for T-DM1 in the adjuvant and neoadjuvant settings is limited, but I predict this will change dramatically over time

The recently completed trials will not be enough and we must develop creative new trials to optimize the use of this effective and well tolerated agent

EPW's Assessment of the State of Affairs



Thank You